Epitomes

Important Advances in Clinical Medicine

Internal Medicine

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The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in internal medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in internal medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association, and the summaries were prepared under the direction of Dr Feinstein and the Panel.

Mild Cobalamin Deficiency

CLASSICAL COBALAMIN DEFICIENCY poses relatively few diagnostic problems today. The patient has megaloblastic anemia and/or neurological dysfunction, a low serum cobalamin level and cobalamin malabsorption (most often secondary to pernicious anemia, the gastric disease in which intrinsic factor secretion is lost). Attention has shifted recently to the challenge of milder cobalamin deficiency states in which signs such as megaloblastic anemia are not apparent. This is a much more common problem than classical deficiency. This entity has emerged largely because of the application of sensitive metabolic tests to patients. These tests include measuring the metabolites methylmalonic acid (MMA) and homocysteine; deoxyuridine suppression testing of bone marrow cells may be more sensitive than measuring metabolite levels, but it is too cumbersome for clinical use.

Whereas homocysteine levels also become abnormal in folate and pyridoxine deficiencies, MMA elevation is more specific for cobalamin deficiency. However, it must be remembered that levels of both metabolites rise with renal insufficiency, volume contraction, various enzyme defects unrelated to vitamin deficiency and, in the case of homocysteine, improper collection and processing of blood samples.

What is the role of the metabolite assays in current clinical practice? Although hyperhomocysteinemia of any cause has important associations with vascular disease, the discussion here will be confined to the issue of cobalamin deficiency. Broadly speaking, metabolite assay has two clinical applications in patients with possible cobalamin deficiency.

One application is in the confirmation of clinically suspected cobalamin deficiency whenever standard tests produce ambiguous results. Examples include the patient with megaloblastic anemia or neurologic dysfunction whose normal or borderline cobalamin levels leave one uncertain whether to pursue other explanations instead. Another example is the patient with megaloblastic anemia who has low serum levels of both cobalamin and folate, leaving one uncertain whether the patient has an "artifactually" low cobalamin level due to folate deficiency alone or is deficient in both vitamins. In both examples, abnormal MMA levels would indicate that cobalamin deficiency is indeed present.

The second application is in the patient who has low cobalamin levels but equivocal or absent clinical signs of deficiency. This situation is more common than either classical deficiency or the situation described in the first set of scenarios. It is especially common in older persons, about 10% of whom (ie, about 4 million Americans) have low cobalamin levels but little or no clinical evidence of deficiency. Evidence from several laboratories indicates that 50–75% of these elderly patients have metabolic evidence of cobalamin deficiency that responds to cobalamin therapy (ie, they have mild, preclinical cobalamin deficiency).

The still unresolved question concerning the latter condition is how much diagnostic and therapeutic effort is warranted by biochemical insufficiency alone. It is fair to say that diagnostic attention and a therapeutic trial are due any patient in whom the entity is uncovered because of symptoms, even vague symptoms. Moreover, even if asymptomatic, any patient found to have an underlying malabsorptive cause must be treated with supplements, especially if the cause of malabsorption is irreversible. For example, 1.9% of 729 healthy elderly people in Los Angeles (including about 4% of elderly white and black women) were found to have untreated, unsuspected and usually asymptomatic pernicious anemia. Like all patients with classical malabsorption, such

patients are best treated with parenteral cobalamin, although large oral doses (1000 μg daily) can be used if necessary. A failure to split cobalamin from its binders in food (food-cobalamin malabsorption), a disorder due to various types of gastric dysfunction including atrophic gastritis and most forms of gastric surgery, is more common than pernicious anemia and has been identified in 30–40% of patients with low cobalamin levels. Such patients can probably be treated with small oral doses of cobalamin (1–10 μg daily), as can patients with nonmalabsorptive causes of deficiency. Treatment of patients with mild cobalamin deficiency may take on added importance as folate supplementation becomes more widespread in the United States.

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Cardiac Troponins in Patients with Chest Pain

BECAUSE THE ELECTROCARDIOGRAM is not diagnostic in almost 50% of patients with acute myocardial infarction (MI), biochemical methods have been crucial for detection of MI in this group. Important characteristics of a reliable serum marker of cardiac necrosis include high concentration in the myocardium, absence in noncardiac tissues, rapid release from injured cells and sufficient persistence in the serum to allow detection after an extended interval from the onset of symptoms. For more than two decades, these criteria have been best met by the myocardial band (MB) isoenzyme of creatine kinase (CK), establishing it as the most widely used serum marker of acute MI. Although CK-MB has been useful, its limitations include lack of specificity due to its presence in noncardiac tissues such as small intestine, skeletal muscle, diaphragm, uterus and prostate and its elevation in renal failure, as well as a pattern of elevation that begins three hours after onset of acute MI and takes up to 12 hours for diagnostic values in many patients. Because CK-MB levels usually return to normal in less than three days in most patients, increased isoenzyme-1 of lactate dehydrogenase (LDH), which also has imperfect specificity but persists for 10–14 days, has been utilized for delayed diagnosis of MI. The limitations of these current biochemical methods have spurred recent interest in new serum markers, much of which has focused on the troponins.

The troponins comprise a protein complex of three subunits that regulates the interaction of actin and myosin in cardiac and skeletal muscle. The subunits are troponin T (cTnT), I (cTnI) and C (cTnC). The amino acid sequences of cTnT and cTnI (but not cTnC) in cardiac and skeletal muscle differ, allowing for a highly specific monoclonal antibody-based assay for their measurement in serum. Early clinical studies of the troponins in the diagnosis of acute MI have revealed a number of advantages over CK-MB. Serum levels of cTnT and cTnI are very low in normal individuals and have greater relative magnitudes of increase in serum after MI than current markers, facilitating the distinction between normal and abnormal data. The sensitivity of cTnT and cTnI for diagnosing acute MI has been equivalent to or higher than that of CK-MB in most studies. Although the time of initial release of the troponins after MI is similar to that of CK-MB, they remain elevated for up to two weeks. The persistence of troponin elevation after infarction will likely render measurement of LDH-1 obsolete for late detection of MI.

A major advantage of the troponins is their superior specificity over CK-MB, reflected in their lack of elevation by injury of noncardiac tissues. This is well demonstrated by normal cardiac troponin levels in marathon runners, in whom CK-MB levels can be elevated. Specificity of cTnI in acute MI is 85–95%. Although the specificity of cTnT has been reported to be as low as 80% in some studies, this may be due to its ability to detect minimal cardiac damage in some patients currently categorized as having unstable angina. Exclusion of the latter group from these studies has resulted in a marked improvement in specificity of cTnT to 95%. One difference between the two cardiac troponins is elevation of cTnT in uremia, which may be related to its detection of uremic myocardial damage.

A growing role for the cardiac troponins has been in the assessment of patients who present to the emergency department without ST-segment elevation on their electrocardiograms. This group includes patients with non-Q MI, unstable angina and chest pain of noncardiac origin. Both cTnI and cTnT obtained in the emergency department have been accurate in identifying those patients in whom acute MI was subsequently diagnosed after admission. Furthermore, elevations of the cardiac troponins in patients with unstable angina have been strong predictors of late cardiac events. The availability of rapid, bedside assays for both cTnT and cTnI have made the troponins an important component of the decision-making process for managing the large group of patients presenting to the emergency department with chest pain of uncertain origin. These early studies must be extended to determine whether the troponins provide additional data beyond the clinical evaluation and electrocardiogram in this important patient population.

The troponins possess superior characteristics as serum markers of myocardial damage compared with current methods. They combine a high degree of sensitivity with greater specificity, more sustained elevation and better prognostic value than current markers and they can be measured by a rapid assay. These factors justify their emerging status as the serum markers of choice